Original Article

Associations of Human Leukocyte Antigen-DRB1 Alleles with Nasopharyngeal Carcinoma and Its Clinical Significance in Xinjiang Uyghur Autonomous Region of China

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Abstract

Background: Genetic susceptibility is one of the major etiological factors for nasopharyngeal carcinoma (NPC). Among the genetic predisposing factors, human leukocyte antigen (*HLA*) genes have been reported to be associated with NPC. This study aimed to investigate the associations of *HLA-DRB1* alleles with NPC and the clinical significance of *HLA-DRB1* alleles in NPC.

Methods: From January 2009 to December 2013, 140 NPC patients (118 Han patients and 22 Uyghur patients) and 158 healthy controls (81 Han individuals and 77 Uyghur individuals) from Xinjiang Province were genotyped for *HLA-DRB1* using the polymerase chain reaction-sequence specific primer technique. Chi-square analysis was used when comparing allele frequencies between groups. The clinical outcomes were evaluated by Kaplan-Meier method and Cox regression model.

Results: Compared with healthy controls, the allele frequency of *HLA-DRB1**0701 was increased in the Uyghur patients ($P = 0.008$) but not in the Han patients ($P = 0.869$). *HLA-DRB1**0101 allele was presented with higher frequency in clinical Stage I + II group compared with clinical Stage III + IV group in the Han patients ($P = 0.015$) but not in the Uyghur patients ($P = 1.000$). Higher frequency of *HLA-DRB1**1501 allele was observed in patients aged <45 years compared with those in patients aged ≥45 years ($P = 0.002$). Neither *HLA-DRB1**0701 nor *HLA-DRB1**0101 had a statistically significant association with 3-year survival.

Conclusions: This study found *HLA-DRB1**0701 in Uyghur population was associated with an increased risk of developing NPC. In Han population, we found *HLA-DRB1**0101 was associated with protection from disease progression, and *HLA-DRB1**1501 was associated with early age of onset. *HLA-DRB1* could not be identified as a prognostic indicator for NPC in either Han or Uyghur patients.

Key words: Human Leukocyte Antigen-DRB1Allele; Nasopharyngeal Carcinoma; Prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant epithelial disease, characterized by its distinctive racial and geographic distribution.[1] It is rare in most parts of the world, but endemic in Southern China with an incidence rate of 20/100,000.[2,3] The major etiological factors include genetic susceptibility, environment factors, and Epstein-Barr virus (EBV) infection.[4] Among all genetic factors, human leukocyte antigen (*HLA*) genes have been shown to have a strong and consistent association with NPC risk.[5] *HLA* polymorphism can alter disease susceptibility and progression in some tumors. The HLA molecules present antigenic peptides to T lymphocyte and modulate the host-tumor immune response.[6] Except for NPC, *HLA* polymorphism has a role in malignant diseases such as breast cancer,[7] hepatocellular carcinoma,[8] lymphoma,[9] and cervical cancer.[10] Different *HLA*-Class I alleles have been reported to be associated with NPC in Southern China. For instance, *HLA-A**02, *-B**46, and *-B**58 increased the susceptibility to NPC, while *HLA-A**11 and *-B**13 showed protections on this disease.[11-15] However,

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few studies focused on the associations of *HLA*-Class II alleles with NPC.

In this study, with the support of clinical data, we were able to investigate the *HLA-DRB1* allele frequencies in NPC patients and healthy controls, as well as in several clinical and pathological subgroups of NPC in Han and Uyghur subjects. Our purpose was to determine whether *HLA-DRB1* alleles are associated with risk of NPC and the role of the *HLA-DRB1* alleles in progress and prognosis of NPC.

Methods

Patients

From January 2009 to December 2013, 140 NPC patients were enrolled in this study from the Affiliated Tumor Hospital of Xinjiang Medical University. All patients' diagnoses were confirmed by clinical pathology. Among these patients, 118 were Han and 22 were Uyghur, and their clinicopathological characteristics are listed in Table 1. The clinical stage of these patients was classified according to the Chinese 2008 staging system.[16] All NPC patients received treatment in compliance with the NCCN Practice Guidelines for Head and Neck Cancer. All 158 healthy controls were recruited from volunteers without a family history of NPC. Among the healthy controls, 81 were Han and 77 were Uyghur. There were 49 males and 32 females in Han subjects (aged from 24 to 78 years) and 50 males and 27 females in Uyghur subjects (aged from 26 to 72 years).

Table 1: The characteristics of all patients with nasopharyngeal carcinoma in this study, *n* (%)

Characteristics	Han patients (*n* = 118)	Uyghur patients (*n* = 22)	χ^2	*P*
Age			2.933	0.087
<45 years	57 (48.3)	15 (68.2)		
≥45 years	61 (51.7)	7 (31.8)		
Gender			0.015	0.903
Male	82 (69.5)	15 (68.2)		
Female	36 (30.5)	7 (31.8)		
EBV infection			–	0.580
EBV-VCA-IgA (+)	114 (96.6)	21 (95.5)		
EBV-VCA-IgA (−)	4 (3.4)	1 (4.5)		
Smoking history			0.093	0.760
Yes	47 (39.8)	8 (36.4)		
No	71 (60.2)	14 (63.6)		
Histological classification			0.317	0.573
Differentiated type of nonkeratinizing SCC	45 (38.1)	7 (31.8)		
Nondifferentiated type of nonkeratinizing SCC	73 (61.9)	15 (68.2)		
T-stage			0.324	0.569
T1–T2	28 (23.7)	4 (18.2)		
T3–T4	90 (76.3)	18 (81.8)		
N-stage			0.945	0.331
N0–N1	45 (38.1)	6 (27.3)		
N2–N3	73 (61.9)	16 (72.7)		
Clinical stage			0.395	0.529
I–II	10 (8.5)	1 (4.5)		
III–IV	108 (91.5)	21 (95.5)		
Treatment			1.013	0.314
Radiotherapy	10 (8.5)	4 (18.2)		
Radiotherapy + chemotherapy	108 (91.5)	18 (81.8)		

EBV: Epstein-Barr virus; VCA: Viral capsid antigen; IgA: Immunoglobulin A; SCC: Squamous cell carcinoma; –: Not applicable.

All participants provided written informed consent before enrollment in this study, and this study was approved by the Institutional Ethics Committee of the Affiliated Tumor Hospital of Xingjiang Medical University.

Genomic DNA extraction

Genomic DNA was extracted from whole blood samples using a Genomic DNA Extraction kit (Bioteke Corp., China) according to manufacturer's instructions. DNA concentration and purity were determined using an ultraviolet spectrophotometer (Thermo Fisher Scientific Inc.,Waltham, MA, USA), the A260/280 ratios were between 1.8 and 1.9, and DNA concentration was adjusted to 0.3–0.5 μg/μl. The DNA samples were stored at −20°C. *HLA-DRB1* genotyping was performed using the polymerase chain reaction-sequence specific primers method.[17]

Epstein-Barr virus-viral capsid antigen-immunoglobulin A detection

Peripheral blood samples were obtained from NPC patients and stored at −20°C. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum EBV-viral capsid antigen (VCA)-immunoglobulin A (IgA). ELISA kits were purchased from the Demeditec Company (Germany).

Follow-up

All patients were required to be followed up after treatment every 3 months. Each follow-up mainly included chest X-ray and magnetic resonance imaging of the nasopharynx, head, and neck areas. Patients who were considered at high risk for distant metastasis received additional computed tomography scans of chest and abdomen, as well as bone scans. Follow-ups were carried out by re-examinations, mailings, and/or telephone calls.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). The allele frequencies between the case and control groups and between different clinical and pathological subgroups were analyzed by the Chi-square test, and two-tailed Fisher's exact test was performed while Chi-square test was not applicable. Odds ratios (*ORs*) were calculated from allelic and genotype frequencies with 95% confidence intervals (*CIs*). Kaplan-Meier method was used to calculate 3-year overall survival (OS), 3-year disease-free survival (DFS), 3-year distant metastasis-free survival (DMFS), and 3-year local relapse-free survival (LRFS). The differences between subgroups were examined by the log-rank test. Univariate Cox regression model was used to evaluate the hazard ratios (*HRs*)

of *HLA-DRB1* and different clinicopathologic factors. A value of $P < 0.05$ was considered statistically significant.

Results

Associations between human leukocyte antigen-*DRB1* and nasopharyngeal carcinoma

Among Uyghur subjects, the *HLA-DRB1**0701 allele frequency in the NPC group was 25.0%, which was significantly higher than that (9.7%) in the healthy controls [Figure 1]; this result suggested that *HLA-DRB1**0701 allele was associated with susceptibility to NPC (*OR* = 3.089, 95% *CI* = 1.300–7.341, *P* = 0.008). Among Han subjects, the *HLA-DRB1**0701 allele frequencies were 11.0% in the NPC group and 10.5% in the healthy controls, without statistically significant difference [*P* = 0.869; Figure 2].

Associations between human leukocyte antigen-DRB1 and clinicopathologic factors

Among Han NPC patients, the *HLA-DRB1**1501 allele frequency in the age group of <45 years was 15.8%, which was significantly higher than that (4.1%) in the age group of ≥45 years (*OR* = 0.228, 95% *CI* = 0.082–0.636, *P* = 0.002; Figure 3); the *HLA-DRB1**0101 allele frequencies were 15.0% in the clinical Stage I + II group and 1.9% in the clinical Stage III + IV group [Figure 4], and the difference between two groups was statistically significant (*OR* = 0.107, 95% *CI* = 0.022–0.517, *P* = 0.015). Among Han NPC patients, there was no statistical difference for the *HLA-DRB1* allele frequencies detected in the subgroups grouped by histological classification, T stage, N stage, and short effects. Among Uyghur NPC patients, although the *HLA-DRB1**1501 allele frequency in the age group of <45 years (6.7%) was lower than that (7.1%) in the age group of ≥45 years, and the *HLA-DRB1**0701 allele frequency in the clinical Stage I + II group (0%) was lower than that (6.3%) in the clinical Stage III + IV group, these differences were not statistically significant (all $P > 0.05$). Similar to the Han NPC patients, there was no statistical difference in *HLA-DRB1* allele frequency detected in the subgroups grouped by histological classification, T stage, N stage, and short effects in Uyghur NPC patients.

Prognostic value of human leukocyte antigen-DRB1 and clinicopathologic factors in nasopharyngeal carcinoma

The median follow-up time of Han patients was 38.5 months (ranging from 3 to 69 months). The median follow-up time of Uyghur patients was 37.0 months (ranging from 5 to 67 months). In the Uyghur patients, both 3-year OS and 3-year LRFS of *HLA-DRB1**0701 group were 66.7%, the 3-year OS and 3-year LRFS of non-*HLA-DRB1**0701 group were 71.1% and 88.9%, respectively. The 3-year OS and 3-year LRFS of *HLA-DRB1**0701 group were lower than those of non-*HLA-DRB1**0701 group, but the differences were not statistically significant [Table 2].

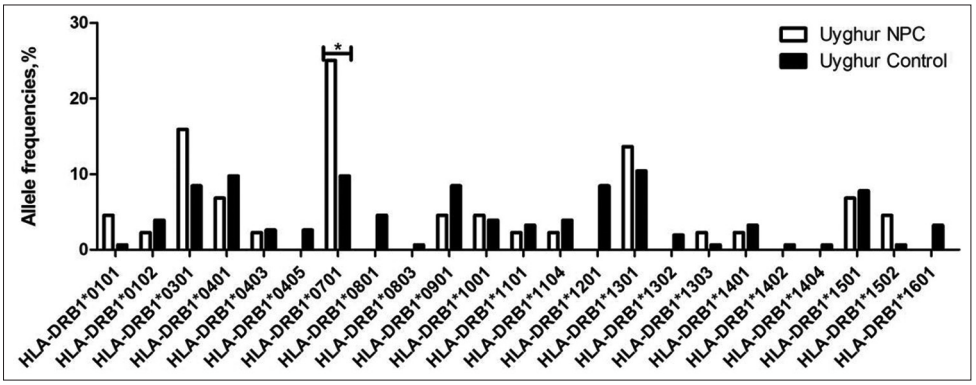

Figure 1: The *HLA-DRB1* allele frequencies between Uyghur NPC patients and Uyghur healthy controls, **P* = 0.008. HLA: Human leukocyte antigen; NPC: Nasopharyngeal carcinoma.

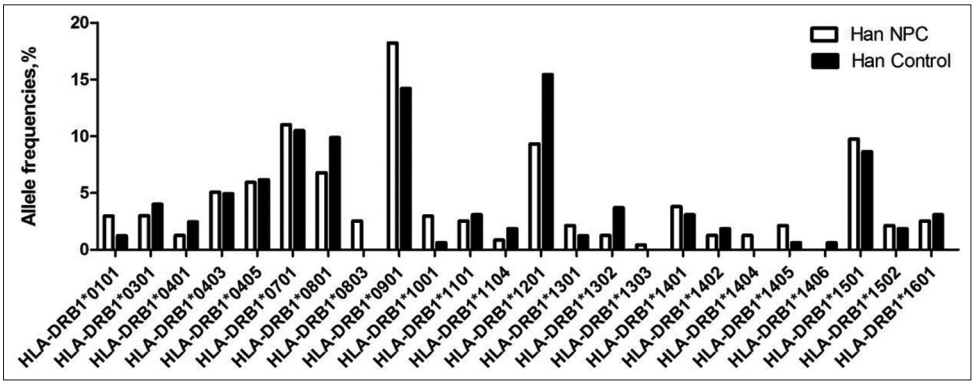

Figure 2: The *HLA-DRB1* allele frequencies between Han NPC patients and Han healthy controls. HLA: Human leukocyte antigen; NPC: Nasopharyngeal carcinoma.

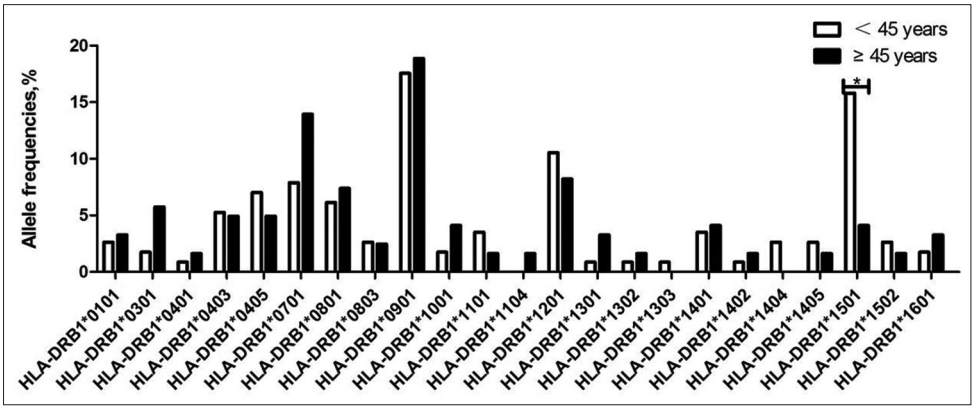

Figure 3: *HLA-DRB1* allele frequencies between age groups of <45 years and ≥45 years in Han patients with nasopharyngeal carcinoma, *$P = 0.002$. HLA: Human leukocyte antigen.

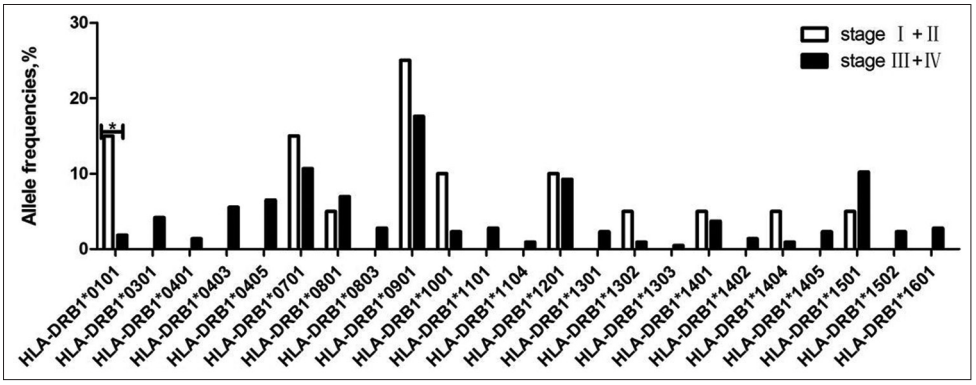

Figure 4: *HLA-DRB1* allele frequencies between clinical Stage I + II group and clinical Stage III + IV group in Han patients with nasopharyngeal carcinoma, *$P = 0.015$. HLA: Human leukocyte antigen.

Table 2: Log-rank analysis of prognostic factors in Uyghur NPC patients ($n = 22$)

Items	Number, *n*	3-year OS (%)	χ^2	*P*	3-year DFS (%)	χ^2	*P*	3-year DMFS (%)	χ^2	*P*	3-year LRFS (%)	χ^2	*P*
*HLA-DRB1**0701 status			0.019	0.891		1.794	0.180		0.215	0.643		0.034	0.854
*HLA-DRB1**0701	11	66.7			78.8			60.6			66.7		
Non-*HLA-DRB1**0701	11	71.1			51.9			50.8			88.9		
Gender			0.669	0.413		0.125	0.724		0.600	0.439		0.325	0.569
Male	15	60.6			67.7			50.3			70.3		
Female	7	80.0			66.7			66.7			80.0		
Age			0.884	0.347		1.515	0.218		1.568	0.211		1.253	0.263
<45 years	15	82.5			76.0			68.1			88.9		
≥45 years	7	50.0			44.4			33.3			50.0		
Histological classification			2.922	0.087		1.273	0.259		2.446	0.118		3.014	0.083
Differentiated type	7	100			83.3			83.3			100		
Nondifferentiated type	15	52.2			58.8			42.6			59.0		
Clinical stage			0.409	0.522		0.427	0.514		0.614	0.433		0.813	0.367
I + II	1	100			100			100			100		
III + IV	21	65.2			64.6			53.5			71.5		
T-stage			0.961	0.327		0.005	0.942		0.039	0.844		1.270	0.260
T1 + T2	4	100			66.7			66.7			100		
T3 + T4	18	62.2			66.6			53.8			69.0		
N-stage			1.116	0.291		0.129	0.720		0.313	0.576		1.431	0.232
N0 + N1	6	100			66.7			66.7			100		
N2 + N3	16	61.7			66.0			53.3			68.4		

NPC: Nasopharyngeal carcinoma; *HLA*: Human leukocyte antigen; OS: Overall survival; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; LRFS: Local relapse-free survival.

Among the Han patients, the 3-year OS of *HLA-DRB1**1501 and non-*HLA-DRB1**1501 groups were 78.5% and 83.6%, respectively, without statistically significant difference [Table 3]. The 3-year OS, DFS, DMFS, and LRFS of *HLA-DRB1**0101 and non-*HLA-DRB1**0101groups were 83.3%, 100%, 100%, 100% and 82.6%, 73.4%, 82.5%, 82.3%, respectively, and there were no statistically significant differences [Table 3]. Univariate Cox regression indicated that *HLA-DRB1* allele and clinicopathological parameters were not predictors for prognosis of Uyghur NPC patients [Table 4]. In the Han population, the clinical stage was a predictor for 3-year OS [*HR* = 2.651, 95% *CI* = 1.182–5.947, *P* = 0.018; Table 5], while other clinicopathological parameters and *HLA-DRB1* allele could not be considered as potential predictors for the prognosis.

Discussion

HLA is the most polymorphic gene complex of all human genetic systems, which consists of more than two hundred genes located close together on chromosome 6 and can be categorized into Class I, Class II, and Class III. The Class I and II molecules display endogenous and exogenous antigens to the immune system, while Class III molecules involve in other immune functions. Different alleles of *HLA* can be a susceptible or protective allele of NPC. Individuals carrying specifically susceptible allele have increasing risk of developing NPC. The variations in susceptibility to NPC might reflect the differences in the anti-EBV capability of HLA haplotypes. Individuals with susceptible *HLA* alleles might not be able to mount enough cytotoxic immune response to eliminate EBV-infected cells.[4] Rubicz *et al*.[18] found the level of anti-EBV EBNA1 IgG is related with *HLA-DRB1* loci, suggesting that specific *HLA* loci might also influence anti-EBV humoral immune response. Most studies of *HLA* alleles and NPC susceptibility investigated the patients in Southern China.[19,20] Recently, Wang *et al*.[21] reported that *HLA-B**46 was significantly associated with NPC in Xinjiang region.

Few studies have been done to investigate the relationship between *HLA*-II alleles and NPC. It has been reported that *HLA-DRB1**0405 is a susceptible allele, and *HLA-DRB1**1501 is a protective allele[22] among Caucasians in America where the incidence rate was low. Different from these low incidence areas, *HLA-DRB1**03 and *HLA-DRB1**13 alleles were demonstrated to be associated with susceptibility to NPC, while *HLA-DRB1**05 was a protective allele in Tunisia (an intermediate incidence area).[23] No associations between the *HLA-DRB1* alleles and NPC were reported in high incidence areas, such as Southern China.[12,24] The correlation between *HLA*-II allele and NPC seemed to be inconsistent in different races from different studies. Here, we reported that in Uyghur population, the *HLA-DRB1**0701 allele frequency in the NPC patients was higher than that in healthy controls (*P* = 0.008),

Table 3: Log-rank analysis of prognostic factors in Han NPC patients (*n* = 118)

Items	Number, *n*	3-year OS (%)	χ^2	*P*	3-year DFS (%)	χ^2	*P*	3-year DMFS (%)	χ^2	*P*	3-year LRFS (%)	χ^2	*P*
*HLA-DRB1**1501 status			0.034	0.853		2.350	0.125		1.970	0.160		2.371	0.124
*HLA-DRB1**1501	23	78.5			89.1			94.7			95.2		
Non-*HLA-DRB1**1501	95	83.6			71.6			81.1			80.6		
*HLA-DRB1**0101 status			0.236	0.627		1.877	0.171		1.187	0.277		1.403	0.236
*HLA-DRB1**0101	7	83.3			100			100			100		
Non-*HLA-DRB1**0101	111	82.6			73.4			82.5			82.3		
Gender			0.455	0.500		0.023	0.880		0.214	0.644		0.008	0.928
Male	82	81.4			73.7			83.0			82.7		
Female	36	85.5			78.4			84.9			85.5		
Age			0.842	0.359		1.168	0.280		0.103	0.749		1.526	0.217
<45 years	57	87.6			80.2			85.4			88.3		
≥45 years	61	77.9			70.0			81.2			79.0		
Histological classification			0.773	0.379		0.292	0.589		0.023	0.879		0.531	0.466
Differentiated type	45	75.1			68.8			81.8			76.3		
Nondifferentiated type	73	87.0			79.4			84.3			88.3		
Clinical stage			1.003	0.317		0.242	0.623		0.476	0.490		0.003	0.953
I + II	10	88.9			76.2			88.9			77.8		
III + IV	108	81.9			75.1			82.9			84.6		
T-stage			0.019	0.889		0.025	0.874		0.057	0.811		0.087	0.768
T1 + T2	28	84.3			74.0			83.3			86.0		
T3 + T4	90	82.0			75.1			83.5			82.6		
N-stage			0.838	0.360		0.026	0.872		0.732	0.392		0.052	0.820
N0 + N1	45	88.3			75.0			87.4			81.8		
N2 + N3	73	78.0			75.1			80.6			85.3		

NPC: Nasopharyngeal carcinoma; *HLA*: Human leukocyte antigen; OS: Overall survival; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; LRFS: Local relapse-free survival.

Table 4: Univariate Cox regression analyses of prognostic factors in Uyghur NPC patients

Factors	3-year OS		3-year DFS		3-year DMFS		3-year LRFS	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
*HLA-DRB1**0701 status		0.891		0.208		0.651		0.857
*HLA-DRB1**0701	1		1		1		1	
Non-*HLA-DRB1**0701	0.882 (0.146–5.311)		2.977 (0.544–16.289)		1.377 (0.344–5.510)		1.180 (0.196–7.117)	
Gender		0.428		0.729		0.455		0.584
Male	1		1		1		1	
Female	0.412 (0.046–3.697)		0.740 (0.135–4.065)		0.543 (0.109–2.699)		0.531 (0.055–5.123)	
Age		0.361		0.242		0.233		0.290
<45 years	1		1		1		1	
≥45 years	2.316 (0.383–14.018)		2.614 (0.524–13.056)		2.332 (0.580–9.386)		2.637 (0.437–15.919)	
Histological classification		0.332		0.292		0.162		0.333
Differentiated type	1		1		1		1	
Nondifferentiated type	42.742 (0.022–84,224.802)		3.188 (0.369–27.580)		4.466 (0.547–36.430)		42.585 (0.021–85,148.450)	
Clinical stage		0.676		0.674		0.617		0.579
I + II	1		1		1		1	
III + IV	22.770 (0.000–5.362×10^7)		22.280 (0.000–4.170×10^7)		22.422 (0.000–4,337,407.866)		29.711 (0.000–4,810,491.419)	
T-stage		0.535		0.943				0.492
T1 + T2	1		1		1	0.847	1	
T3 + T4	26.478 (0.001–834,943.116)		0.925 (0.108–7.931)		1.229 (0.151–10.001)		29.732 (0.002–478,273.514)	
N-stage		0.509		0.725		0.589		0.470
N0 + N1	1		1		1		1	
N2 + N3	27.888 (0.001–538,949.647)		1.471 (0.171–12.629)		1.783 (0.219–14.541)		30.767 (0.003–332,472.900)	

NPC: Nasopharyngeal carcinoma; *HLA*: Human leukocyte antigen; OS: Overall survival; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; LRFS: Local relapse-free survival; *HR*: Hazard ratio; *CI*: Confidence interval.

and the patients carrying *HLA-DRB1**0701 allele had a 3-fold risk of developing NPC (*OR* = 3.089, 95% *CI* = 1.300–7.341). This *HLA-DRB1**0701 allele might serve as a susceptible allele in Uyghur population. Similar to the researches from high incidence areas, we also found no associations between *HLA-DRB1* allele with NPC in Han population. The previous study's ethnic origin was from Southern China,[24] our research focused on Xinjiang region including Han and Uyghur populations. The *HLA-DRB1* allele distribution in Uyghur population was different from Han population,[25] which might be due to the difference between the two ethnicities. Moreover, we also detected the EBV VCA-IgA level in Han and Uyghur NPC patients and found no statistically significant difference between these two groups, which indicated the different frequency distribution of *HLA-DRB1* between two ethnicities might have no relation with EBV infection.

There are several reports on the relationships between *HLA*-Class II alleles and the clinicopathologic characteristics of some malignant tumors. The frequency of *HLA-DQB1**07 allele was reported to be significantly higher in early nonsmall cell lung cancer (NSCLC) than that in advanced cancer.[26] The above studies indicated that *HLA* alleles can influence in the disease development and severity, and further affect treatment outcome. Our study found that among Han NPC patients, *HLA-DRB1**1501 and *HLA-DRB1**0101 alleles were associated with age and clinical stage, respectively, but not with gender, histology, T stage, N stage, and short effects. In our study, the frequency of *HLA-DRB1**1501 allele in the age group of <45 years was higher than that in the age group of ≥45 years (*OR* = 9.158, 95% *CI* = 0.082–0.636, *P* = 0.002), suggesting this allele might contribute to the age of onset in Han NPC patients. In addition, our study found that *HLA-DRB1**0101 was associated with clinical stage in the Hans, which indicated that this allele might play a role in the pathogenesis of Han NPC patients. Among Uyghur NPC patients, no associations were found between *HLA-DRB1* with clinicopathologic factors including histological classification, T stage, N stage, clinical stage, and short effects. Moreover, further investigation on these aspects is needed.

Both *HLA*-Class I and Class II alleles were reported to be associated with survival in some tumors. *HLA-DRB1**01 and *HLA-DRB1**02-null were reported to be associated with shorter OS in chronic lymphocytic leukemia.[27] In a study of malignant lymphoma, *HLA-Cw**0701 was found to be associated with poorer OS in patients with diffuse large B-cell lymphoma, and *HLA-A**0101 was associated with poorer OS, while *HLA-DRB1**13 and *HLA-B*Bw4* were associated with better OS in patients with follicular lymphoma.[28] From a research on 695 NSCLC patients in Japan, *HLA-A**02 was indicated as an unfavorable prognostic factor in the Stage I NSCLC and *HLA-A**24 as an unfavorable prognostic factor in Stage II + III NSCLC.[29]

Table 5: Univariate Cox regression analyses of prognostic factors in Han NPC patients

Factors	3-year OS		3-year DFS		3-year DMFS		3-year LRFS	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
*HLA-DRB1**1501 status		0.854		0.145		0.194		0.159
*HLA-DRB1**1501	1		1		1		1	
Non-*HLA-DRB1**1501	1.107 (0.374–3.275)		2.931 (0.690–12.452)		3.816 (0.506–28.806)		4.276 (0.567–32.282)	
*HLA-DRB1**0101 status		0.632		0.372		0.478		0.440
*HLA-DRB1**0101	1		1		1		1	
Non-*HLA-DRB1**0101	1.633 (0.219–12.150)		22.518 (0.024–20,897.672)		22.295 (0.004–118,492.478)		22.718 (0.008–63,328.617)	
Gender		0.632		0.881		0.646		0.928
Male	1		1		1		1	
Female	1.633 (0.219 –12.150)		0.935 (0.390–2.240)		0.769 (0.251–2.360)		1.049 (0.370–2.979)	
Age		0.364		0.285		0.750		0.225
<45 years	1		1		1		1	
≥45 years	1.483 (0.634–3.471)		1.547 (0.695–3.447)		1.168 (0.450–3.030)		1.851 (0.684–5.007)	
Histological classification		0.384		0.591		0.880		0.470
Differentiated type	1		1		1		1	
Nondifferentiated type	0.688 (0.297–1.595)		0.805 (0.365–1.775)		1.080 (0.399–2.922)		0.704 (0.271–1.825)	
Clinical stage		0.018		0.626		0.501		0.953
I + II	1		1		1		1	
III + IV	2.651 (1.182–5.947)		1.433 (0.338–6.082)		2.002 (0.265–15.102)		0.957 (0.218–4.193)	
T-stage		0.889		0.875		0.812		0.769
T1 + T2	1		1		1		1	
T3 + T4	0.936 (0.366–2.393)		0.932 (0.389–2.233)		1.146 (0.373–3.516)		1.183 (0.386–3.632)	
N-stage		0.365		0.873		0.398		0.820
N0 + N1	1		1		1		1	
N2 + N3	1.496 (0.626–3.571)		1.067 (0.484–2.353)		1.536 (0.568–4.160)		0.895 (0.345–2.324)	

NPC: Nasopharyngeal carcinoma; *HLA*: Human leukocyte antigen; OS: Overall survival; DFS: Disease-free survival; DMFS: Distant metastasis-free survival; LRFS: Local relapse-free survival; *HR*: Hazard ratio; *CI*: Confidence interval.

Our study found that *HLA-DRB1* allele had no prognostic value in either Han or Uyghur population which suggested that its role in prognosis should be further elucidated.

In conclusion, our findings indicated that *HLA-DRB1**0701 was a genetic predisposing factor for NPC in Uyghur population. *HLA-DRB1**0101 influenced NPC disease progression and *HLA-DRB1**1501 might contribute to the low morbidity of NPC in Han population. *HLA-DRB1* could be identified as a prognostic indicator for NPC neither in Han patients nor in Uyghur patients. *HLA-DRB1* alleles could potentially be valuable for the evaluation of risk for NPC and its disease progression.

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Conflicts of interest

There are no conflicts of interest.

References

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 2006;15:1765-77. doi: 10.1158/1055-9965.EPI-06-0353.
2. Huang TR, Zhang SW, Chen WQ, Deng W, Zhang CY, Zhou XJ, *et al.* Trends in nasopharyngeal carcinoma mortality in China, 1973-2005. Asian Pac J Cancer Prev 2012;13:2495-502. doi: 10.7314/APJCP. 2012.13.6.2495.
3. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol 2002;12:421-9. doi: 10.1016/S1044579X02000858.
4. Tsao SW, Yip YL, Tsang CM, Pang PS, Lau VM, Zhang G, *et al.* Etiological factors of nasopharyngeal carcinoma. Oral Oncol 2014;50:330-8. doi: 10.1016/j.oraloncology.2014.02.006.
5. Hildesheim A, Wang CP. Genetic predisposition factors and nasopharyngeal carcinoma risk: A review of epidemiological association studies, 2000-2011: Rosetta Stone for NPC: Genetics, viral infection, and other environmental factors. Semin Cancer Biol 2012;22:107-16. doi: 10.1016/j.semcancer.2012.01.007.
6. Finn OJ. Cancer immunology. N Engl J Med 2008;358:2704-15. doi: 10.1056/NEJMra072739.
7. Atoum MF, Tanashat RQ, Mahmoud SA. Negative association of the HLA-DQB1*02 allele with breast cancer development among Jordanians. Asian Pac J Cancer Prev 2013;14:7007-10. doi: 10.7314/APJCP. 2013.14.11.7007.
8. Pan N, Chen K, Qiu J, Sun H, Xu J, Miao F, *et al.* Human leukocyte antigen class I alleles and haplotypes associated with primary hepatocellular carcinoma in persistent HBV-infected patients. Hum Immunol 2013;74:758-63. doi: 10.1016/j.humimm.2013.02.007.
9. McAulay KA, Jarrett RF. Human leukocyte antigens and genetic susceptibility to lymphoma. Tissue Antigens 2015;86:98-113. doi: 10.1111/tan.12604.
10. Zhang X, Lv Z, Yu H, Wang F, Zhu J. The HLA-DQB1 gene polymorphisms associated with cervical cancer risk: A meta-analysis. Biomed Pharmacother 2015;73:58-64. doi: 10.1016/j.biopha.2015.06.002.
11. Tian W, Zhu FM, Wang WY, Cai JH, Zhang W, Li LX, *et al.* Sequence-based typing of HLA-A gene in 930 patients with

nasopharyngeal carcinoma in Hunan province, Southern China. Tissue Antigens 2015;86:15-20. doi: 10.1111/tan.12576.
12. Hildesheim A, Apple RJ, Chen CJ, Wang SS, Cheng YJ, Klitz W, *et al.* Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 2002;94:1780-9. doi: 10.1093/jnci/94.23.1780.
13. Hu SP, Day NE, Li DR, Luben RN, Cai KL, Ou-Yang T, *et al.* Further evidence for an HLA-related recessive mutation in nasopharyngeal carcinoma among the Chinese. Br J Cancer 2005;92:967-70. doi: 10.1038/sj.bjc.6602347.
14. Yu KJ, Gao X, Chen CJ, Yang XR, Diehl SR, Goldstein A, *et al.* Association of human leukocyte antigens with nasopharyngeal carcinoma in high-risk multiplex families in Taiwan. Hum Immunol 2009;70:910-4. doi: 10.1016/j.humimm.2009.08.005.
15. Tang M, Zeng Y, Poisson A, Marti D, Guan L, Zheng Y, *et al.* Haplotype-dependent HLA susceptibility to nasopharyngeal carcinoma in a Southern Chinese population. Genes Immun 2010;11:334-42. doi: 10.1038/gene.2009.109.
16. Pan J, Xu Y, Qiu S, Zong J, Guo Q, Zhang Y, *et al.* A comparison between the Chinese 2008 and the 7th edition AJCC staging systems for nasopharyngeal carcinoma. Am J Clin Oncol 2015;38:189-96. doi: 10.1097/COC.0b013e31828f5c96.
17. Hu J, Li L, Pang L, Chen Y, Yang L, Liu C, *et al.* HLA-DRB1*1501 and HLA-DQB1*0301 alleles are positively associated with HPV16 infection-related Kazakh esophageal squamous cell carcinoma in Xinjiang China. Cancer Immunol Immunother 2012;61:2135-41. doi: 10.1007/s00262-012-1281-x.
18. Rubicz R, Yolken R, Drigalenko E, Carless MA, Dyer TD, Bauman L, *et al.* A genome-wide integrative genomic study localizes genetic factors influencing antibodies against Epstein-Barr virus nuclear antigen 1 (EBNA-1). PLoS Genet 2013;9:e1003147. doi: 10.1371/journal.pgen.1003147.
19. Hassen E, Nahla G, Bouaouina N, Chouchane L. The human leukocyte antigen class I genes in nasopharyngeal carcinoma risk. Mol Biol Rep 2010;37:119-26. doi: 10.1007/s11033-009-9548-9.
20. Li X, Fasano R, Wang E, Yao KT, Marincola FM. HLA associations with nasopharyngeal carcinoma. Curr Mol Med 2009;9:751-65. doi: 10.2174/156652409788970698.
21. Wang R, Hu Y, Yindom LM, Huang L, Wu R, Wang D, *et al*. Association analysis between HLA-A, -B, -C, -DRB1, and -DQB1 with nasopharyngeal carcinoma among a Han population in Northwestern China. Hum Immunol 2014;75:197-202. doi: 10.1016/j.humimm.2013.12.015.
22. Burt RD, Vaughan TL, McKnight B, Davis S, Beckmann AM, Smith AG, *et al*. Associations between human leukocyte antigen type and nasopharyngeal carcinoma in Caucasians in the United States. Cancer Epidemiol Biomarkers Prev 1996;5:879-87.
23. Makni H, Daoud J, Ben Salah H, Mahfoudh N, Haddar O, Karray H, *et al.* HLA association with nasopharyngeal carcinoma in Southern Tunisia. Mol Biol Rep 2010;37:2533-9. doi: 10.1007/s11033-009-9769-y.
24. Li PK, Poon AS, Tsao SY, Ho S, Tam JS, So AK, *et al.* No association between HLA-DQ and -DR genotypes with nasopharyngeal carcinoma in Southern Chinese. Cancer Genet Cytogenet 1995;81:42-5. doi: 10.1016/0165-4608(94)00205-3.
25. Shen CM, Zhu BF, Deng YJ, Ye SH, Yan JW, Yang G, *et al.* Allele polymorphism and haplotype diversity of HLA-A, -B and -DRB1 loci in sequence-based typing for Chinese Uyghur Ethnic Group. PLoS One 2010;5:e13458. doi: 10.1371/journal.pone.0013458.
26. Bulut I, Meral M, Kaynar H, Pirim I, Bilici M, Gorguner M. Analysis of HLA class I and II alleles regarding to lymph node and distant metastasis in patients with non-small cell lung cancer. Lung Cancer 2009;66:231-6. doi: 10.1016/j.lungcan.2009.01.012.
27. Lech-Maranda E, Juszczynski P, Szmigielska-Kaplon A, Jamroziak K, Balcerczak E, Robak T. Human leukocyte antigens HLA DRB1 influence clinical outcome of chronic lymphocytic leukemia? Haematologica 2007;92:710-1. doi: 10.3324/haematol.10910.
28. Lu Y, Abdou AM, Cerhan JR, Morton LM, Severson RK, Davis S, *et al.* Human leukocyte antigen class I and II alleles and overall survival in diffuse large B-cell lymphoma and follicular lymphoma. Scientific World Journal 2011;11:2062-70. doi: 10.1100/2011/373876.
29. Nagata Y, Hanagiri T, Mizukami M, Kuroda K, Shigematsu Y, Baba T, *et al.* Clinical significance of HLA class I alleles on postoperative prognosis of lung cancer patients in Japan. Lung Cancer 2009;65:91-7. doi: 10.1016/j.lungcan.2008.10.012.